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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	14

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,004	ANDERSON ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19 and 25-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-19 and 25-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

The amendment filed March 6, 2003 is acknowledged and has been entered.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 13 recites the affinity column comprises recombinant, microorganism display antibodies or fragments thereof. On page 6, lines 10-17 of the specification, Applicant provides a list of immunologic and non-immunological affinity materials. However, recombinant, microorganism display antibodies or fragments thereof are not disclosed in the specification.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 10 and 11 recites reverse phase stationary phase is a non-porous C18 material. On page 6, lines 4-6 of the specification, Applicant discloses that conditions such as, but not limited to, for example, pH, mesh size, flow rates and stationary phase media selection can be modified to select for specific low molecular weight patterns. However, reverse phase stationary phase is a non-porous C18 material is not disclosed anywhere in the specification.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On page 32, lines 11-18 in the specification. The applicant discloses methods for fractionation of native urinary proteins. The applicant does not disclose all native proteins. There is no description in the specification for all native proteins (i.e. serum, plasma).

3. Claims 26 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. On page 19, lines 4-6 in the specification. The applicant discloses that the normal kidney retains proteins above approximately 55 kd, and those of lower mass would be expected to be filtered out through the kidney and should appear in the urine. On page 42, lines 15-22 in the specification. The applicant discloses the Fractionation of urine proteins on the basis of their native molecular weight by using a Superdex 75 gel filtration column that generates two fractions, one >30 kDa and one < 30 kDa. The applicant does not disclose the filtration limits of a normal kidney is about 30,000 daltons. There is no description in the specification that the filtration limits of a normal kidney is about 30,000 daltons.

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 3-19 and 25-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 the recitation "above about" is vague and indefinite. It is unclear what applicant intends. There is no definition provided for the term in the specification.

Claim 1 the recitation "the filtration limits of a normal kidney" there is insufficient antecedent basis for this limitation.

Claim 29, the recitation "plural specific predetermined proteins" is vague and indefinite. Does this mean that the affinity column binds many of the same kind of protein or many different proteins and if it binds many different proteins how is this done?

Claim 32 is vague and indefinite because it is a product by process claim and it seems to be directed to claim 1 which is a method of detecting al least one low molecular weight protein and/or peptide component in a biological fluid. Furthermore, since claim 1 is a method of detecting and claim 32 is a fractionation of a biological sample, it is unclear of the dependency of claim 32. Does claim 32 actually depend from claim 1 or is it an independent claim?

Claim 38 is vague and indefinite because it is unclear where in the process is the step of contacting a test biological fluid with said antibody against at least one of said proteins or peptides is occurring. Does it occur after step (a) or step (b) or step (c)?

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 3-5, 30-34 and 36 rejected under 35 U.S.C. 102(b) as being anticipated by Lie et al (US 5,492,834) in light of Gilbert et al (US 6,402,913).

Liu et al disclose a method for detecting proteins in urine and serum samples. Liu et al disclose applying the sample to a size exclusion gel to fractionate proteins. Liu et al disclose separating and recovering the components. Liu et al disclose that the sample is fractionated and eluted, and the eluent is collected (i.e. recovered) (col 8, lines 30-34). Liu et al disclose processes for separating and determining at least one analyte having a specific analyte molecular weight range. Liu et al disclose that the analyte of interest can be alpha-1- antitrypsin (a protein with a molecule weight above 3 kDa and below the filtration limits of a normal kidney). Liu et al disclose that that any technique or procedure suitable for separating, identifying and/or quantitating proteins is suitable for their method (col 8, lines 63-67).

Gilbert et al disclose that Alpha-1- antitrypsin is a protein of 54 kDa (col 1, line 55).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of O'Donnell et al (US 5,998,216)

See above for teachings of Liu et al and Gilbert et al.

Liu et al and Gilbert et al differ from the instant invention in failing to teach the addition of at least one protease inhibitor to the body fluid upon collection.

O'Donnell et al disclose the addition of protease inhibitor to urine. O'Donnell et al disclose that the addition of protease inhibitors to urine provides for maintaining and preserving the integrity of proteins and polypeptides present in a body fluid sample obtained ex-vivo (abstract). O'Donnell et al also disclose that these protease inhibitors provide a powerful effect on cytokines individually and collectively in human urine samples; and enhances markedly the stability and the preservation effect for the cytokines under a variety of different collection and environmental conditions (col 13, lines 1-56).

It would have been obvious to one of ordinary skill in the art to incorporate the use of a protease inhibitor such as taught by O'Donnell et al into the method of Liu et al because O'Donnell et al shows the addition of protease inhibitors to urine provides for

maintaining and preserving the integrity of proteins and polypeptides present in a body fluid sample obtained ex-vivo. O'Donnell et al also disclose that these protease inhibitors provide a powerful effect on cytokines individually and collectively in human urine samples; and enhances markedly the stability and the preservation effect for the cytokines under a variety of different collection and environmental conditions.

7. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Anderson et al (Analytical techniques for cell fractions, Analytical Biochemistry 95, 48-61 (1979).

See above for teachings of Liu et al and Gilbert et al.

Liu et al and Gilbert et al differ from the instant invention in failing to teach the use of centrifugation.

Anderson et al disclose methods for concentrating urinary proteins. Anderson et al disclose centrifuging the urine sample (p. 52). Anderson et al disclose that centrifuging the urine provides for removal of high molecular weight materials such as DNA and other very high molecular weight substances that would plug acrylamide gels.

It would have been obvious to one of ordinary skill in the art to incorporate centrifugation of the urine sample as taught by Anderson et al into the method of Liu et al because Anderson et al shows that centrifugation provides for removal of high molecular weight materials such as DNA and other very high molecular weight substances that would plug acrylamide gels.

8. Claims 10, 11 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Opiteck et al (Two-Dimensional

SEC/RPLC Coupled to Mass Spectrometry for the Analysis of Peptides, Anal. Chem. 1997, 69, 2283-2291).

See above for teachings of Liu et al in view of Gilbert et al.

Liu et al and Gilbert et al differ from the instant invention in failing to specifically teach fractionating said first fraction by elution from a reverse phase stationary phase and identifying proteins or peptides by mass spectrometry.

Opiteck et al disclose methods for fractionating, separating, recovering and determining peptides. Opiteck et al disclose further fractionating a fraction by reversed phase liquid chromatography, which utilizes nonporous C-18 modified silica particles, which produce fast and efficient analyses. Opiteck also disclose identifying the peptide by mass spectrometry. Opiteck disclose that the use of RPLC and mass spectrometry provided for fast and efficient analyses of protein samples.

It would have been obvious to one of ordinary skill in the art to incorporate reversed phase liquid chromatography and mass spectrometry into the method of Liu et al because Liu et al specifically teach that any technique or procedure suitable for separating, identifying and/or quantitating proteins is suitable for their method (col 8, lines 63-67) and further, because Opiteck shows that the use of RPLC and mass spectrometry provided for fast and efficient analyses of protein samples.

9. Claims 12, 15-17, 27 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Hage et al (Affinity Chromatography: A Review of Clinical Applications, Clinical Chemistry 45:5 593-615, 1999).

See above for teachings of Liu et al and Gilbert et al.

Liu et al and Gilbert et al differ from the instant invention in failing to teach further fraction from an affinity column.

Hage et al disclose methods comprising biological-like interactions for the separation and specific analysis of sample components. Hage et al disclose immunoaffinity columns and non-immunological affinity columns such as protein G and protein A. Hage et al disclose that affinity chromatography is rapidly becoming the separation method of choice in clinical laboratories and other biologically related fields such as pharmaceutical science and biotechnology. Hage et al disclose that affinity chromatography is an attractive alternative to traditional methods for the selective quantification and study of clinical samples and provides for the creation of an affinity system for almost any compound of clinical interest.

It would have been obvious to one of ordinary skill in the art to incorporate affinity chromatography as taught by Hage et al into the method of Liu et al because Liu et al specifically teach that any technique or procedure suitable for separating, identifying and/or quantitating proteins is suitable for their method (col 8, lines 63-67) and further, because Hage et al shows that affinity chromatography is an attractive alternative to traditional methods for the selective quantification and study of clinical samples and provides for the creation of an affinity system for almost any compound of clinical interest.

10. Claims 13, 14 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Hage et al as applied to claims 1, 3-5, 12, 15-17, 29-34 and 36 and further in view of McCombs et al (Us 5,114,863).

See above for teachings of Liu et al, Gilbert et al, and Hage et al.

Liu et al, Gilbert et al and Hage et al differ from the instant invention in failing to teach the antibody is directed to alpha-1-antitrypsin and the generation of an antibody directed to alpha-1-antitripsin.

McCombs et al disclose specific binding reagents such as antibodies directed to alpha-1-antitrypsin.

It would have been obvious to one of ordinary skill in the art to generate and use the alpha-1-antityrpsin specific antibodies taught by McCombs et al in the modified method of Liu et al because Hage et al is generic with respect to the analyte that is to be separated and one would use the appropriate reagent, i.e. antibody for the desired analyte, in this case alpha-1-antitrypsin.

11. Claims 6 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Furst et al (US 5,926,387).

See above for teachings of Liu et al and Gilbert et al.

Liu et al and Gilbert differ from the instant invention in failing to teach zonal sedimentation centrifugation on density gradients.

Furst et al disclose a technique, which, involves layering a sample containing the components of interest onto the top of a liquid column, which is stabilized by a

density-gradient of an inert solute. Furst et al disclose that this process is known as Rate-zonal sedimentation. Rate-zonal sedimentation is used to improve the efficiency of the fractionation by separating the particles according to size (col 1, lines 45-67).

It would have been obvious to one of ordinary skill in the art to incorporate rate-zonal sedimentation as taught by Furst et al into the method of Liu et al because Furst et al shows that rate-zonal sedimentation improves the efficiency of the fraction by separating the particles according to size.

With respect to the stationary phases comprising different mesh sizes as recited in the instant claims, the mesh sizes can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

Response to Arguments

Applicant's arguments filed March 6, 2003 have been fully considered but are not found persuasive.

Applicant argues that the amendments to the specification reflect the elements recited in claims 10, 11 and 13. This is not found persuasive because of reasons stated above under the section entitled Specification.

Applicant argues that the term "above about" is not per se indefinite and that a keyword search for U.S. Patents limited to claims (1976 – present) show that 6608 issued U.S. patents recite the term "above about" in the claims and thus, "above about" is a well-recognized term of art. This is not found persuasive because the merits of the case are treated on an individual basis and in the instant application there is no definition provided for the term in the specification. The specification on p. 42, lines 15-18 discloses that fractionation range is 3 – 75 kDa. The specification does not disclose above about 3. Further, Applicant recites " a molecular weight above about 3 kDa and below the filtration limits of a normal kidney. Thus the interpretation of the range is broad and arbitrary. Therefore, it is unclear what applicant intends by the recitation "above about" and thus, the rejection is maintained.

Applicant argues that the recitation "the filtration limits of a normal kidney" has been taken out of context in the Action and is in fact being used by applicants to define a range of molecular weights of proteins embraced by the claims. This is not found persuasive. However, it is suggested to delete "the" and replace with –a-- to overcome the rejection. Also, applicant argues that the filtration limits of a normal kidney is well know and that a search limited to the specification for filtration limits of the normal kidney in the patent database would result in 11 hits. However, the specification on page 19 defines the filtration limits as 55 kDa.

Applicant argues that the Liu et al reference does not teach a method comprising "separating a fraction having proteins or peptides with a molecular weight above about 3 kDa and below the filtration limits of a normal kidney," nor recovery of proteins from this separated fraction. These arguments have been noted but are not found persuasive. The instant claims recite fractionating, separating and recovering without any specific steps. Therefore, the Liu reference is seen to anticipate the instant claims because Liu teaches fractionating a sample into different components, separating and recovering (col 8, lines14-69) by specifically reciting that the sample is fractionated and eluted (column 8, lines 14-25), and the eluent is collected, i.e. recovered (column 8, lines 30-34. This eluent comprises the excluded and suitably fractionated components (i.e. the first fraction). Liu further teaches that the collected eluent (i.e. the fractionated and separated first fraction) is recovered by collecting and storing it for later analysis or immediately analyzed for the analytes of interest (column 8, lines 52-62). Liu specifically teach that their method comprises processes for separating and determining at least one analyte having a specific analyte molecular weight range. Such processes include pretreating a sample and then separating the eluent components and detecting the analyte of interest (col 8, lines 55-59). With respect to the molecular weight above about 3 kDa and below the filtration limits of a normal kidney. Liu et al teach the protein may be alpha-1-antitrypsin (54 kDa) which falls within the range. Because, by way of applicant's own disclosure on page 19 in the specification, the normal filtration cutoff of the kidney is 55 kDa. Therefore, Liu et al teaches a protein with a molecular weight above about 3 kDa and below the filtration limits of a normal kidney.

Conclusion

12. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (703) 305-1444. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703)308-4242 for regular communications and (703)3084242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gary Counts
Examiner
Art Unit 1641
April 29, 2003

LONG V. LE
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04/29/03